Osemab™
(D e n o s u m a b)

اوسیمیب

Solution for Injection 120mg/1.7mL

DESCRIPTION
Osemab contains Denosumab. Denosumab is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Osemab (Denosumab) Solution for Injection is available for subcutaneous administration as:

Osemab Solution for Injection 120mg/1.7mL
Each single dose 1.7mL vial contains:
Denosumab...120mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

Pharmacokinetics
Absorption
Following subcutaneous administration, bioavailability was 62%.

Distribution
Denosumab displayed nonlinear pharmacokinetics at doses below 60mg, but approximately dose-proportional increases in exposure at higher doses. With multiple subcutaneous doses of 120mg once every 4 weeks, up to 2.8-fold accumulation in serum Denosumab concentrations was observed and steady-state was achieved by 6 months. A mean (± standard deviation) serum steady-state trough concentration of 20.5 (± 13.5) mcg/mL was achieved by 6 months.

Metabolism
Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination
In patients with advanced cancer who discontinued doses of 120mg every 4 weeks, the mean half-life was 28 days (range: 14 to 55 days).

THERAPEUTIC INDICATIONS
Osemab (Denosumab) is indicated for the:
- Prevention of skeletal-related events in adults with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

DOSAGE AND ADMINISTRATION
Important Administration Instructions
- Osemab (Denosumab) should be administered under the responsibility of a healthcare provided.
- Osemab (Denosumab) is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally.
- Osemab (Denosumab) injection is a clear, colorless to pale yellow solution supplied in a single-dose vial.
- Product is for single-use in one patient only.
- Supplementation of at least 500mg calcium and 400IU vitamin D daily is required in all patients, unless hypercalcemia is present.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Osemab (Denosumab) is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter.
- The entire contents of the vial should be injected.

Recommended Doses
Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
The recommended dose of Osemab (Denosumab) is 120mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia.

Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
The recommended dose of Osemab (Denosumab) is 120mg administered every 4 weeks with additional 120mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia. Patients with giant cell tumor of bone should be evaluated at regular intervals to determine whether they continue to benefit from treatment.

Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy
The recommended dose of Osemab (Denosumab) is 120mg administered every 4 weeks with additional 120mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen.

Special Population
Renal impairment
No dose adjustment is required in patients with renal impairment.

Hepatic impairment
The safety and efficacy of Denosumab have not been studied in patients with hepatic impairment.

Elderly patients (age ≥ 65)
No dose adjustment is required in elderly patients.

Pediatric
The safety and efficacy of Osemab (Denosumab) have not been established in pediatric patients (age < 18) other than skeletally mature adolescents (aged 12-17 years) with giant cell tumor of bone.

ADVERSE REACTIONS
Very Common
Hypocalcemia, dyspnea, diarrhea and musculoskeletal pain.

Common
New primary malignancy, hypophosphatemia, tooth extraction, hyperhidrosis and osteonecrosis of the jaw.

Uncommon
Hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone, lichenoid drug eruptions and atypical femoral fracture.

Rare
Drug hypersensitivity and anaphylactic reaction.

Not known
Osteonecrosis of the external auditory canal.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Denosumab is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipient of the product.
- Severe, untreated hypocalcemia.
- Unhealed lesions from dental or oral surgery.
- Pregnancy.

PRECAUTIONS
Concomitant Treatment with other Denosumab-Containing Medicinal Products
Patients being treated with Denosumab should not be treated concomitantly with other Denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumors).

Hypersensitivity
Clinically significant hypersensitivity including anaphylaxis has been reported with Denosumab. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Denosumab.

Hypocalcemia
Denosumab can cause severe hypocalcemia and fatal cases have been reported. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Denosumab. Adequately supplement all patients with calcium and vitamin D. Patients with advanced chronic kidney disease [i.e., eGFR <30mL/min/1.73m^2] including dialysis-dependent patients are at greater risk for severe hypocalcemia following Denosumab administration. The presence of underlying chronic kidney disease-mineral bone disorder (CKD-MBD, renal osteodystrophy) markedly increases the risk of hypocalcemia. Concomitant use of calcimimetic drugs may also worsen hypocalcemia risk. Instruct all patients with advanced chronic kidney disease, including those who are dialysis-dependent, about the symptoms of hypocalcemia and the importance of maintaining serum calcium levels with adequate calcium and activated vitamin D supplementation.

Osteonecrosis of the Jaw (ONJ)
Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Denosumab. Osteonecrosis of the jaw, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. A routine oral exam should be performed by the prescriber prior to initiation of Denosumab treatment. Good oral hygiene practices should be maintained during treatment with Denosumab. Concomitant administration of drugs associated with ONJ may increase the risk of developing ONJ. The risk of ONJ may increase with duration of exposure to Denosumab.
For patients requiring invasive dental procedures and who are suspected of having or who develop ONJ while on Denosumab, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient or discontinuation of treatment based on individual benefit-risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical low energy or low trauma fractures of the shaft have been reported in patients receiving Denosumab. During Denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Denosumab therapy should be considered, pending a benefit-risk assessment, on an individual basis.

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons
Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in Denosumab-treated patients with giant cell tumor of bone and patients with growing skeletons.
Hypercalcemia has been reported within the first year after treatment discontinuation. After treatment is discontinued, monitor patients for signs and symptoms of hypercalcemia, assess serum calcium periodically, reevaluate the patient's calcium and vitamin D supplementation requirements and manage patients as clinically appropriate. Denosumab is not recommended in patients with growing skeletons.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Denosumab Treatment
Following discontinuation of Denosumab treatment, fracture risk increases, including the risk of multiple vertebral fractures. New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of Denosumab. Prior vertebral fracture was a predictor of multiple vertebral fractures after Denosumab discontinuation. Evaluate an individual's benefit-risk before initiating treatment with Denosumab. If Denosumab treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.

Embryo-Fetal Toxicity
Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use effective contraception.

Osteonecrosis of the External Auditory Canal
Osteonecrosis of the external auditory canal has been reported with Denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving Denosumab who present with ear symptoms including chronic ear infections.

Pregnancy
Denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with Denosumab. Any effects of Denosumab are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Nursing Mother
It is unknown whether Denosumab is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made on whether to abstain from breast-feeding or to abstain from Denosumab therapy taking into account the benefit of breast-feeding to the newborn/infant and the benefit of therapy for the woman.

DRUG INTERACTIONS
Bisphosphonates
Patients being treated with Denosumab should not be treated concomitantly with bisphosphonates.

OVERDOSAGE
There is no experience with overdose in clinical studies. Denosumab has been administered in clinical studies using doses up to 180mg every 4 weeks (cumulative doses up to 1,080mg over 6 months), and no additional adverse reactions were observed. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

STORAGE
Store in refrigerator at 2°C to 8°C. Do not freeze.
Protect from direct light and heat.
Prior to administration, Osemab may be allowed to reach room temperature up to 25°C in the original carton.
Once removed from refrigerator, the vial can be used for up to 30 days when stored below 25°C.
Avoid vigorous shaking.
Discard unused portion.
Keep in the original carton to protect from light.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Osemab (Denosumab) Solution for Injection 120mg/1.7mL is available in pack of 1's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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